EXTERNAL RESPONSIVE NEUROSTIMULATION SYSTEM EFFECTS ON POWER AND COHERENCE SPECTRA OF INTRACRANIAL ELECTROENCEPHALOGRAPHY

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INTRODUCTION

A novel implantable closed-loop Responsive Neurostimulation System (RNS, Neuropace Inc, Mountain View, CA) consisting of a pulse generator, subdural strip/depth electrodes and programmer is undergoing a prospective, pivotal multicenter clinical trial. RNS continuously analyzes electrocorticograms (ECoGs) and automatically applies electrical stimulation when specified epileptiform activity is detected. This study has shown that RNS is safe for patients and can reduce partial seizure frequency and severity. However, the exact mechanism of action of RNS is unknown.

There have been no published quantitative analyses of EEG with RNS. Power spectrum and coherence analyses of the electroencephalogram (EEG) have often been used to study brain dysfunction, including epilepsy. Power spectra demonstrate relative power of regional cortical activity at a broad range of frequencies. Coherence, a measure of cross-correlation of inter-regional frequency content, implies changes in functional connectivity, which can be more useful than time domain and power spectral analyses in assessing responsiveness to anti-seizure therapy. In this study, we analyze acute effects of RNS on interictal ECoG power spectra and coherence.

The purpose of this study is to determine the effects of RNS on quantitative intracranial EEG to further elucidate potential mechanisms of action of this emerging mode of therapy for epilepsy.

METHODS

Subjects and experimental conditions: Five adult patients with refractory seizures were admitted to the epilepsy monitoring unit for intracranial EEG monitoring for epilepsy surgery evaluation. ECoG was recorded with subdural and depth electrodes placed in the most active cortical regions, as determined by prior EEG scalp recordings and intraoperative ECoG. All patients were on stable anticonvulsants during this time period.

An externalized RNS (eRNS, Neuropace, Mountain View, CA) device was connected to the most active intracranial electrodes for epileptiform activity detection. The epileptiform activity detection algorithm used was designed to detect spikes. The eRNS was programmed to apply brief stimulation trains to specified electrodes in response to detected epileptiform discharges with pre-defined characteristics (e.g., amplitude, duration, waveform shape, frequency) above specified thresholds. The thresholds were set such that the patient received cortical stimulation (125 Hz, 2 mA, 10 sec) at least every 5 minutes during periods with increased epileptiform activity. Therefore, each patient received at least several hundred, and up to several thousand stimuli during the monitoring/treatment period.

Continuous ECoG data were recorded using the XLTEK system (Oakville, Ontario, Canada). The sampling frequency was 500 Hz. Frequencies below 1 Hz and above 100 Hz were removed by digital filtering. These recordings were reviewed by an electroencephalographer who selected artifact free data segments (e.g., from eye and body movements, EMG and ambient electrical noise) during the awake state prior to connecting the eRNS and immediately following a 12 hour to greater than 24 hour period of intermittent RNS stimulation for analysis.

Data analysis: EEG signals were reviewed and data recorded from electrodes without significant artifact were analyzed. Power spectral and coherence analyses were computed from sampled intracranial EEG data from each individual electrode recorded during wakefulness using multi-taper methods of spectral analysis. Each data segment provided an estimate of the power spectrum for each electrode location and coherence profile between each electrode pair for the awake state during the pre-eRNS and post-eRNS periods. In this analysis the pre-eRNS and post-eRNS power spectra and coherence were compared for regions with the greatest interictal epileptiform activity. We examined power spectra at frequencies ranging from 0 to 100 Hz from each EEG channel. *Power spectra* summarize the frequency content of the time-varying EEG signal and index the relative strength of contribution of particular frequencies to the overall composite signal. The *coherence* of two signals provides a measure of cross-correlation in the frequency domain and can be thought of as an index of dynamic interaction of two signals as a function of frequency (Bendat and Piersol, 2000). The coherence is computed from the cross spectrum at a given frequency *f* normalized by the power spectra of each signal (using the square root of the sum of their squares, see Eq. 6 below). Thus obtaining peaks or troughs in the coherence is not simply the result of a strong local maximum or minimum within a frequency range of one or the other power spectrum (e.g., see middle Results panel).

Power and coherence spectra were computed using Matlab v. 6.5 with the multi-taper method (Thomson and Chave 1991, Mitra and Pesaran 1999) on 1 second swatches of data sampled at 500 Hz. Three Slepian data tapers were used for the power spectra and seven for the coherence spectra. The multi-taper method is based on the use of multiple orthogonal data tapers to stabilize the variance and optimize the bias of a spectral estimate. A direct estimate of the power spectrum, $S_{MT}(f)$—(Eq. 2), is calculated using this method by averaging over individual tapered spectral estimates:

$$\tilde{x}_k(f) = \sum_{1}^{N} w_t(k) x_t \exp(-2\pi i f t) \qquad (1)$$

The weights *wt* represent the sequence of orthogonal data tapers, *xt* is the signal. The estimate of the power spectrum is obtained by averaging over the tapered estimates:

$$S_{MT}(f) = \frac{1}{K} \sum_{k=1}^{K} \left| \tilde{x}_k(f)^2 \right| \qquad (2)$$

The coherence spectrum, *C*(*f*), is similarly obtained from multi-taper estimates of the power spectra from two signals (S1 and S2 , see Eq. 6 below). To calculate confidence limits for our spectra we use jackknife methods as developed by Thomson and Chave (1991). The logarithm of the power spectrum at a single frequency is used to stabilize the estimation procedure. Delete-one jackknife estimates are formed as in (3) and their average (4) to obtain a spectrum estimate. The jackknife estimate of the variance of the log power spectrum is given by (5). Using these quantities it is possible to construct confidence intervals for the power spectra and coherence estimates shown on the poster (see Thomson and Chave 1991). Coherence estimates at a frequency *f* are computed as shown in Eq. 6.

$$\ln \hat{S}_{\hat{j}} = \ln\left(\frac{1}{N-1} \sum_{\substack{i=1,\\ i \neq j}}^{N} \hat{S}_i \right) \qquad (3)$$

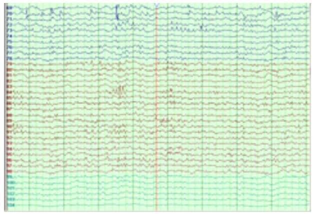
$$\ln \hat{S}_{\cdot} = \ln\left(\frac{1}{N-1} \sum_{\substack{i=1,\\ i \neq j}}^{N} \hat{S}_{\hat{j}} \right) \qquad (4)$$

$$\hat{\sigma}^2 = \operatorname{var}\{\ln \hat{S}\} = \frac{N-1}{N} \sum_{i=1}^{N} (\ln \hat{S}_{\hat{j}} - \ln \hat{S}_{\cdot})^2 \qquad (5)$$

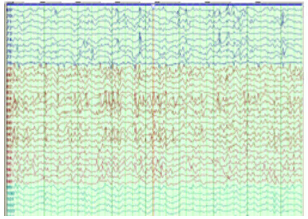
$$\hat{C}_{\hat{j}}(f) = \frac{\sum_{\substack{i=1,\\ i \neq j}}^{N} \hat{S}_i^1(f) \hat{S}_i^2(f)}{\sum_{\substack{i=1,\\ i \neq j}}^{N} \left| \hat{S}_i^1(f) \right|^2 \sum_{\substack{i=1,\\ i \neq j}}^{N} \left| \hat{S}_i^2(f) \right|^2} \qquad (6)$$

Patient 1

Pre-Stimulation ECoG



Post-Stimulation ECoG

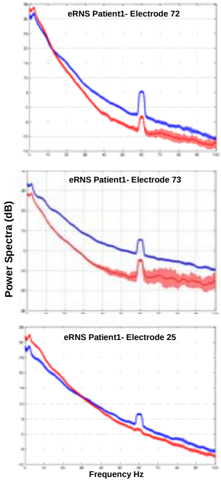


Pre- and post-RNS awake EEG segments from Patient 1 revealing prominent interictal spikes in channels 70 and 71, prior to connection with the RNS. The occurrence of epileptiform discharges was not decreased in these channels after eRNS for 29 hours.

ECoG Power Spectra

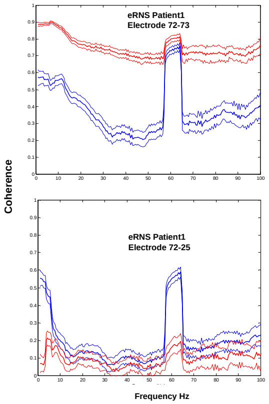
🟦 Pre-stimulation

🟥 Post-stimulation



After RNS ON a broad reduction in power occurred in the inferior temporal electrodes with more frequent epileptiform discharges (72 > 73) in Patient 1. In contrast, electrode (25) with less frequent epileptiform activity in the ipsilateral parieto-occipital region showed a slight increase in power below 20 Hz after RNS for 29 hours.

ECoG Coherence



For patient 1 the coherence was significantly increased between the electrodes near the epileptic focus that was stimulated for all frequencies after RNS for 29 hours. There was a significant decrease in coherence at lower frequencies (< 5 Hz) between the active and distant electrodes.

Patient 2

Pre-Stimulation ECoG

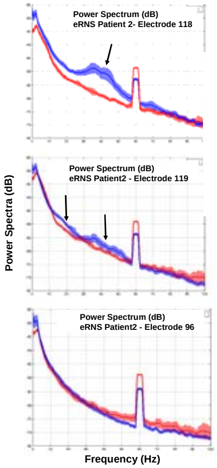
Post-Stimulation ECoG

Pre- and post-RNS awake EEG segments from Patient 2 revealing prominent interictal spikes in channels 115 and 116, which were connected to the RNS. The occurrence of epileptiform discharges was significantly decreased after eRNS for a 25 hour period.

ECoG Power Spectra

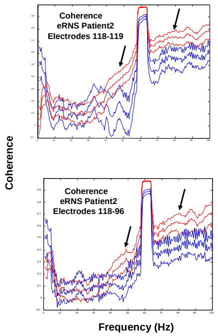
🟦 Pre-stimulation

🟥 Post-stimulation



After RNS ON for 25 hours a broad reduction in power occurred in anterior temporal electrodes with very frequent epileptiform discharges (118 > 119) in Patient 2. In contrast, electrode (96) with much less frequent epileptiform activity in the ipsilateral mid-parietal region showed a slight increase in power above 45 Hz after RNS for 25 hours.

ECoG Coherence



For patient 2 the coherence was significantly decreased in the lower frequencies (1-5 Hz) after RNS for 25 hours, and was significantly increased at higher frequencies (>45 Hz).

RESULTS

- ➢ In most patients a broad reduction in ECoG power occurred after the RNS ON period compared with the pre-stimulation period. This change was most prominent and over a greater bandwidth near the epileptic focus, where the stimulus was applied.
- ➢ In most patients coherence between adjacent electrode pairs was also changed after eRNS, but the pattern of change (i.e., increase vs. decrease, degree, bandwidth) was variable between patients.
- ➢ The greatest degree of change in coherence occurred between the electrodes closest to the active epileptic focus that was stimulated, although changes were noted in distant electrodes also.

CONCLUSIONS

- ➢ RNS had similar effects on ECoG power spectra (i.e., a decrease in power) for most patients most prominently near the epileptic focus.
- ➢ ECoG coherence changed after RNS for most patients, also most prominently near the seizure focus. However, the direction was different for some of the patients at certain frequency bands. This may reflect different effects of RNS in individual patients.
- ➢ These quantitative ECoG findings are similar to those from our earlier study of epileptic patients receiving acute vagus nerve stimulation. (Kobylarz et al. AES Abstract, 2004).
- ➢ These findings support the utility of using quantitative EEG (i.e., power spectra and coherence) to assess the effects of neurostimulation therapies for epilepsy.
- ➢ The changes in intra- and inter-regional ECoG frequency content could reflect neuromodulatory effects from neurostimulation.
- ➢ Further ECoG frequency analyses to determine different patterns of change with RNS in regions adjacent to and remote from epileptic foci may yield specific patterns, potentially providing information to elucidate the mechanism(s) of action of cortical neurostimulation for the treatment of epilepsy, which has not yet been precisely determined.
- ➢ Further quantitative ECoG analyses could help elucidate what response patterns can predict RNS efficacy as well as for parameter optimization.

ACKNOWLEDGEMENTS

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